IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC, Defendants.	C.A. No. 19-2017 (RGA) (SRF) (Consolidated)

MSN'S OPENING POST-TRIAL FINDINGS OF FACT

George C. Lombardi
Bryce A. Cooper
Kurt A. Mathas
Jason Z. Pesick
Kevin J. Boyle
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601-9703
(312) 558-5600

Noorossadat Torabi
WINSTON & STRAWN LLP
101 California Street, 35th Floor
San Francisco, CA 94111-5840
(415) 591-1000

Dominick T. Gattuso (#3630)
HEYMAN ENERIO GATTUSO & HIRZEL LLP
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorneys for Defendants
MSN Laboratories Private Limited and
MSN Pharmaceuticals, Inc.

Dated: June 21, 2022

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

Term	Definition
'473 patent	U.S. Patent No. 7,579,473
DTX	Defendants Trial Exhibit
Egan	William J. Egan, et al., "Prediction of Drug Absorption Using Multivariate Statistics," J. Med. Chem., Vol. 43, pp. 3867-3877 (2000)
Exelixis	Plaintiff Exelixis, Inc.
Fry	D.W. Fry, et al., "Specific, Irreversible Inactivation of the Epidermal Growth Factor Receptor and erbB2, by a New Class of Tyrosine Kinase Inhibitor," Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 12022-12027 (1998)
HCC	Hepatocellular carcinoma
JTX	Joint Trial Exhibit
Kelner	M.J. Kelner, et al., "Anti-leukemic action of the novel agent MGI 114 (HMAF) and synergistic action with topotecan," published in Leukemia, Vol. 14, pp. 136-141 (2000)
Kirin Publication	English Translation of International Publication WO 03/000660
Lipinski	Christopher A. Lipinski, et al., "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," Advanced Drug Delivery Reviews, Vol. 23, pp. 3-25 (1997)
Maulik	G. Maulik, et al., "Role of the hepatocyte growth factor receptor, c-Met, in oncogenesis and potential for therapeutic inhibition," Cytokine & Growth Factor Reviews, Vol. 13, Issue 1, pp. 41-59 (2002)
McMorris	Trevor C. McMorris, et al., "Structure and Reactivity of Illudins," Tetrahedron, Vol. 45, No. 17, pp. 5433-5440 (1989)
MSN Laboratories	Defendant MSN Laboratories Private Limited
MSN Pharmaceuticals	Defendant MSN Pharmaceuticals Inc.
MSN	MSN Laboratories and MSN Pharmaceuticals
NCCN	National Comprehensive Cancer Network
Oliff	A. Oliff, et al., "New Molecular Targets for Cancer Therapy", Scientific American, pp. 144-149 (1996)
Onderwater 1998	Rob C.A. Onderwater, et al., "Cytotoxicity of a series of mono- and di-substituted thiourea in freshly isolated rat hepatocytes: a preliminary structure-toxicity relationship study," Toxicology, Vol.

Term	Definition
	125, Vol. 125, pp. 117-129 (1998)
Onderwater 1999	Rob C.A. Onderwater, et al., “Activation of Microsomal Glutathione S-Transferase and Inhibition of Cytochrome P450 1A1 Activity as a Model System for Detecting Protein Alkylation by Thiourea-Containing Compounds in Rat Liver Microsomes,” Chem. Res. Toxicol., Vol. 12, pp. 396-402 (1999)
OPEX	Operating expense
POSA	Person of ordinary skill in the art
RCC	Renal cell carcinoma
Salaün	J. Salaün, “Cyclopropane Derivatives and their Diverse Biological Activities,” Topics in Current Chemistry, Vol. 207, pp. 1-67 (2000)
Shawver	Laura K. Shawver et al., “Smart drugs: Tyrosine kinase inhibitors in cancer therapy”, Cancer Cell, Vol. 1, at pp. 117-123 (2002)
Silverman	The Organic Chemistry of Drug Design and Drug Action, by R. B. Silverman, Academic Press (1992)
Thomas	Fundamentals of Medicinal Chemistry: An Introduction, by Gareth Thomas, John Wiley & Sons (2000)
TKI	Tyrosine kinase inhibitor
Traxler	Peter Traxler “Tyrosine kinases as targets in cancer therapy-successes and failures”, Expert Opin. Ther. Targets, Vol. 7, Issue 2, pp. 215-234 (2003)
Williams	D. Lyn H. Williams and Ling Xia, “Evidence for the Enol form of Malonamide,” J. Chem. Soc., Chem. Commun., pp. 985-986 (1992)

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Dr. Salvatore Lepore	Live	Dr. Lepore is MSN's expert in the field of medicinal chemistry. He testified regarding the obviousness of the asserted claim 5 of the '473 patent.
Dr. Anthony Mega	Live	Dr. Mega is MSN's expert in the field of medical oncology. He testified regarding the motivation to target c-Met, and in response to the alleged failure of others and long-felt, unmet need.
Dr. Robert DeForest McDuff	Live	Dr. McDuff is MSN's expert in evaluating economics of the pharmaceutical industry. He testified in response to the alleged commercial success.
Dr. David MacMillan	Live	Dr. MacMillan is Exelixis's expert in the field of organic and medicinal chemistry. He testified regarding the nonobviousness of the asserted claim 5 of the '473 patent.
Dr. Daniel James George	Live	Dr. George is Exelixis's expert in the field of treatment of cancer, including evaluation of existing and potential new treatments for renal cell carcinoma. He testified regarding the motivation to target c-Met, failure of others, and long-felt, unmet need.
Michael Tate	Live	Mr. Tate is Exelixis's expert in the field of economic analysis as it pertains to commercial success. He testified regarding the commercial success.
Dr. Lynne Bannen	By Deposition	Dr. Bannen is one of the named inventors of the '473 patent.
Dr. Larry Mann	By Deposition	Dr. Mann is one of the named inventors of the '473 patent.

I. BACKGROUND

A. Parties

1. Exelixis brought actions for patent infringement against MSN Laboratories and MSN Pharmaceuticals. D.I. 270-1 (Uncontested Facts) at ¶ 1.

2. Exelixis is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1851 Harbor Bay Parkway, Alameda, CA 94502. *Id.* at ¶ 2.

3. MSN Laboratories is a corporation organized and existing under the laws of India, having its principal place of business at MSN House, Plot No: C-24, Industrial Estate, Sanath Nagar, Hyderabad, Telangana, India, 500018. *Id.* at ¶ 3.

4. MSN Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 20 Duke Road, Piscataway, NJ 08854. *Id.* at ¶ 4. MSN Pharmaceuticals is a wholly owned subsidiary of MSN Laboratories. *Id.* at ¶ 5.

B. The ’473 Patent

5. The ’473 patent is titled “c-Met Modulators and Methods of Use” and was duly and legally issued on August 25, 2009 and expires on August 14, 2026. D.I. 270-1 (Uncontested Facts) at ¶¶ 12, 14.

6. MSN does not dispute that Exelixis owns the ’473 patent. *Id.* at ¶ 13.

7. Exelixis has asserted claim 5 of the ’473 patent against MSN. *Id.* at ¶ 15.

8. Claim 5 of the ’473 patent recites the compound cabozantinib or its pharmaceutically acceptable salt. *Id.* at ¶¶ 16-17, 19; JTX-3.208.

9. The priority date for claim 5 of the ’473 patent is September 26, 2003. D.I. 270-1 (Uncontested Facts) at ¶ 22.

10. Claim 5 does not recite any properties of cabozantinib. Lepore Tr. at 410:17-19; MacMillan Tr. at 729:18-22.

11. Cabozantinib includes a geminal cyclopropyl substituted malonamide group. Lepore Tr. at 411:7-20; MacMillan Tr. at 670:4-19, 671:6-13.

12. Cabozantinib inhibits certain tyrosine kinases, including c-Met. Lepore Tr. at 410:20-411:6; MacMillan Tr. at 668:11-16.

II. LEVEL OF ORDINARY SKILL IN THE ART

13. The definition of a POSA applied by MSN's experts for the purposes of the asserted claim 5 of the '473 patent-in-suit is provided in Paragraph 24 of the Uncontested Facts Exhibit to the Final Pretrial Order. D.I. 270-1.

14. The definition of a POSA applied by Exelixis's experts is provided in Paragraph 23 of the Uncontested Facts Exhibit to the Final Pretrial Order. D.I. 270-1.

15. The opinions offered by each side's experts do not change based on which of the above definitions of a POSA is applied. Lepore Tr. at 412:19-22; Mega Tr. at 519:1-14; MacMillan Tr. at 664:4-6; George Tr. at 537:24-538:1.

III. TECHNICAL BACKGROUND

A. Cancer Drug Development

16. The prior art taught several molecular defects leading to cancer. Mega Tr. at 520:5-17; DTX-66.1.

17. As the Oliff reference explained, knowledge of these molecular defects enabled researchers to develop targeted therapies for treating cancer. Mega Tr. at 520:18-521:5; DTX-66.1.

18. Defective or aberrant tyrosine kinases were known to cause various cancers. Mega Tr. at 522:11-13.

19. The prior art taught that tyrosine kinases were attractive and "druggable" targets for cancer drug development. Mega Tr. at 522:14-523:9; DTX-17.1-2.

20. Before September 2003, many companies were pursuing TKIs to develop cancer therapeutics. MacMillan Tr. at 730:11-14; Geroge Tr. at 591:6-11.

21. A spectrum selective TKI is an inhibitor that targets and inhibits more than one tyrosine kinase. Mega Tr. at 524:24-525:5.

22. Gleevec was one of the earlier spectrum selective TKIs that received FDA approval before September 2003 and turned a lethal cancer (chronic myelogenous leukemia) to a treatable one. Mega Tr. at 523:11-524:3; George Tr. at 565:9-15, 591:19-592:5; DTX-17.2, 3 (Table 2). The approval of Gleevec was an exciting time in the medical field, because it was the first time there was clinical evidence of successfully treating a cancer by targeting a specific defective tyrosine kinase. George Tr. at 592:6-13. Gleevec's success motivated researchers to look for more TKIs for treating other cancers. George Tr. at 592:14-17.

23. Other TKIs received approval as cancer treatments shortly thereafter, George Tr. at 592:18-21, and a number of other TKIs were in development. For example, by September 2003, Herceptin had been approved to treat breast cancer. George Tr. at 564:17-20. Other small molecule TKIs, including Iressa and Tarceva, had been approved to treat cancer, or were in phase III clinical trials as of the 2003 publication of the prior art Traxler paper. DTX-17.3 (Table 2); George Tr. at 565:24-566:7.

24. By September 2003, most of the compounds in clinical development for treatment of cancer were spectrum selective TKIs. Mega Tr. at 525:6-526:12; DTX-17.3 (Table 2); George Tr. at 591:12-15.

25. The NCCN is a consortium of cancer centers and institutions that send representatives for various disease states to review data and then provide guidelines for treatment options for various cancers, such as RCC. Mega Tr. at 789:4-15; George Tr. at 545:19-546:2. They are foundational in providing care to cancer patients and are integral to medical education. Mega Tr. at 789:16-22; George Tr. at 547:19-25.

26. Different treatment options are categorized in two different ways. Mega Tr. at 790:17-791:18; DTX-118.27. The treatment options are differentiated (i) based on the level of evidence and consensus that supports the Guideline's recommendations, as indicated by numbers 1, 2A, 2B, and 3, and (ii) based on the level of preference, as indicated by "Preferred intervention," "Other recommended interventions," and "Useful in certain circumstances". Mega Tr. at 790:17-791:18; DTX-118.27.

27. Category 1 represents highest level of evidence and uniform NCCN consensus (85% or higher) that the intervention is appropriate. Mega Tr. at 790:17-791:18; DTX-118.27. Category 2 represents lower level of evidence, with 2A representing 85% or higher NCCN consensus, and 2B representing between 50-85% consensus, that the intervention is appropriate. Mega Tr. at 790:17-791:18; DTX-118.27.

28. The level of preference in the NCCN Guidelines are determined based on factors such as efficacy, safety, toxicity, affordability, accessibility, and the level of evidence for each intervention. Mega Tr. at 790:17-791:18; DTX-118.27.

B. Small Molecule Drug Design

29. As of September 2003, drugs were designed starting from lead compounds with promising properties. Lepore Tr. at 413:10-25; DTX-14.50; MacMillan Tr. at 726:7-24.

30. A POSA would have then worked on optimizing the lead compound's properties, including potency and oral bioavailability, while minimizing toxicity. Lepore Tr. at 413:18-25, 414:13-23, 418:22-419:5; DTX-14.50; MacMillan Tr. at 666:4-15, 726:25-727:3, 742:20-24.

31. A POSA would have measured a compound's potency by determining the concentration at which the compound inhibits 50% of the target, i.e., the IC_{50} value. Lepore Tr. at 415:1-14; McMillan Tr. at 666:22-667:2.

32. A more potent compound has a smaller IC_{50} value. Lepore Tr. at 415:1-14; MacMillan Tr. at 667:3-8.

33. Before September 2003, oral bioavailability was known as one of the most desirable attributes of a drug candidate. Lepore Tr. at 415:15-416:11; DTX-22.2.

34. To predict a compound's oral bioavailability, the prior art disclosed a popular, simple, and descriptive method called "Rule of 5," developed by Lipinski. Lepore Tr. at 415:20-416:11; DTX-22.2; MacMillan Tr. at 752:5-17. The popularity of Lipinski's Rule of 5 is reflected in the number of times it has been cited by others in the field: hundreds of times before September 2003, and thousands of times by 2021. Lepore Tr. at 417:12-418:3; MacMillan Tr. at 752:15-17.

35. The Rule of 5 sets forth four criteria for predicting a compound's oral bioavailability. Lepore Tr. at 416:12-417:3; DTX-20.7.

36. Using the Rule of 5 would have been within the skill of a POSA. MacMillan Tr. at 751:14-17; Lepore Tr. at 416:12-417:11.

37. As implemented at Pfizer at the time, when a medicinal chemist registered a new compound, a computer-generated alert would notify the medicinal chemist that the compound might be poorly orally bioavailable if two out of the four criteria fell outside the limits set by the Rule of 5. Lepore Tr. at 418:4-13; DTX-20.7.

38. Adding an oxygen atom (O) to water (H_2O) to obtain hydrogen peroxide (H_2O_2) changes the compound's properties. MacMillan Tr. at 668:1-10. But this is not a small change, as Dr. MacMillan agreed this change nearly doubles the molecular weight of the compound. MacMillan Tr. at 730:5-9.

C. Irreversible Inhibitors

39. Drugs may inhibit their biological targets reversibly or irreversibly. Lepore Tr. at 419:10-17; MacMillan Tr. at 712:23-713:19. When an irreversible inhibitor binds to its target, it forms a covalent bind with the target, and thus it would inhibit the target in a permanent way. Lepore Tr. at 419:10-420:24; MacMillan Tr. at 712:23-713:19. When a reversible inhibitor binds to its target, it can come off the target, and thus the inhibition would not be permanent. Lepore Tr. at 419:10-420:24; MacMillan Tr. at 712:23-713:19.

40. The prior art disclosed several advantages of irreversible inhibitors. Lepore Tr. at 420:25-421:3. For example, the Silverman textbook taught that smaller and fewer doses were often needed to achieve the same effect when using irreversible inhibitors compared to reversible inhibitors. Lepore Tr. at 421:4-23; DTX-13.194.

41. Dr. MacMillan agreed that a POSA would have understood that developing an irreversible inhibitor would be "wonderful". MacMillan Tr. at 731:15-20.

42. Irreversible TKIs were in phase 2 clinical trials before September 2003. Lepore Tr. at 423:4-424:5; DTX-17.3 (Table 2); Geroge Tr. at 591:16-18.

43. The prior art taught the potential advantageous properties of irreversible TKIs over reversible TKIs, e.g., minimizing multiple dosing requirements, fewer nonspecific interactions, and reduced toxicity. Lepore Tr. at 421:24-422:24, 424:6-13; DTX-30.5.

D. Cyclopropane And Cyclopropyl Containing Compounds

44. Cyclopropyl is a three-carbon ring, which is the smallest ring that can be formed. Lepore Tr. at 424:14-425:2; MacMillan Tr. at 760:21-761:1.

45. The prior art taught compounds containing a cyclopropyl group were of great general interest to synthetic and bioorganic chemists as they had a variety of biological properties, including antitumor properties. Lepore Tr. at 425:8-426:5; DTX-28.2.

IV. CLAIM 5 WOULD HAVE BEEN OBVIOUS IN VIEW OF THE PRIOR ART

A. A POSA Would Have Been Motivated To Look For c-Met Inhibitors

46. It is undisputed that by September 2003, a POSA would have been motivated to develop therapies that target and inhibit c-Met for treating cancer. Lepore Tr. at 463:18-24; Mega Tr. at 529:3-17; George Tr. at 594:17-19.

47. There is no dispute that the prior art disclosed c-Met as one of the tyrosine kinases under evaluation for drug development for treating renal cancer. Mega Tr. 526:22-527:8; DTX-17.2 (Table 1); MacMillan Tr. at 732:7-9; George Tr. at 596:2-18.

48. Dr. Geroge agreed that Shawver discussed c-Met as a new therapeutic target for cancer treatment and that "[c]linically, HGF/Met overexpression has been shown to correlate with poor prognosis in several types of cancer." George Tr. at 599:18-600:7, 600:20-22; DTX-39.5.

49. Maulik taught mutations (or molecular defects) in c-Met were well described in certain human cancers. Mega Tr. at 528:6-25; DTX-37.2.

50. Dr. George agreed that Maulik taught inhibitors of the c-Met pathway "have drawn much interest." George Tr. at 602:3-6; DTX-37.15.

51. It is undisputed that c-Met was known in the art as "an attractive target for molecularly targeted therapy in a variety of solid tumors and hematological malignancies and

designs of small molecule inhibitors and antibodies against c-Met would be clinically useful." Mega Tr. at 529:1-10; DTX-37.16; George Tr. at 603:20-604:9.

52. The Kirin Publication would have further motivated a POSA to look for c-Met inhibitors because it taught c-Met inhibitors could be useful as antitumor agents. Lepore Tr. at 428:22-430:9; DTX-6.4. Dr. MacMillan agreed. MacMillan Tr. at 675:18-21; 732:19-733:6.

53. Dr. MacMillan agreed that the Kirin Publication disclosed small molecules that inhibit c-Met, including potent c-Met inhibitors with potent antitumor activity. McMillan Tr. at 675:18-21, 732:19-733:6.

54. It is undisputed that the motivation to develop new TKIs extended beyond targeting Her2, EGFR, VEGFR2, tyrosine kinases targeted by Gleevec, Herceptin and first generation TKIs. Mega Tr. at 527:12-528:5; DTX-39.5; George Tr. at 598:24-599:13.

55. Exelixis's experts agreed the prior art did not discourage targeting c-Met or testing c-Met inhibitors as potential cancer therapy. George Tr. at 606:3-11; MacMillan Tr. at 733:7-11.

B. Kirin Example 5 Would Have Been An Obvious Lead Compound

56. It is undisputed that a POSA motivated to develop therapies that target and inhibit c-Met would have selected a lead compound from the Kirin Publication. Lepore Tr. at 431:1-5; MacMillan Tr. at 735:10-13. This is because the Kirin Publication was the only prior art that disclosed specific exemplified small molecule c-Met inhibitors with corresponding bioactivity. Lepore Tr. at 430:20-25, 470:18-471:8. Dr. MacMillan agreed. MacMillan Tr. at 735:5-9.

57. While the general formula disclosed in the Kirin Publication could encompass millions of compounds, Dr. MacMillan admitted that a POSA would not have started with these millions of compounds to select a lead compound. MacMillan Tr. at 738:1-10.

58. Instead, a POSA would have looked at the IC_{50} data for the 333 exemplary compounds in Table 2 of the Kirin Publication and would have evaluated the more potent compounds to select a lead compound. Lepore Tr. at 431:15-432:18; MacMillan Tr. at 725:5-19.

59. When selecting a lead compound, a POSA would have been motivated to minimize toxicity. Lepore Tr. at 418:22-419:5, 433:2-8.

60. The prior art taught thiourea compounds with similar structure to the Kirin Publication thiourea compounds were toxic. Lepore Tr. at 433:9-434:3, 436:22-437:11, 505:2-10; DTX-19.2.

61. For example, Onderwater 1998 taught that metiamide, a compound with a thiourea functional group, was removed from the market due to bone marrow toxicity. Lepore Tr. at 434:4-21; DTX-18.2. Metiamide, like Kirin Example 1 and other thiourea compounds in the Kirin Publication, contains a di-substituted thiourea functional group. Lepore Tr. at 434:22-435:10.

62. Further, the most toxic compound disclosed and tested in Onderwater 1998, the N, N'-diphenyl thiourea, is the most similar compound to the thiourea compounds in the Kirin Publication. Lepore Tr. at 435:11-436:21; DTX-18.8 (Table 2).

63. Dr. MacMillan agreed that some thiourea containing compounds were known to be toxic, and a POSA would not have been able to predict which thiourea compounds would be toxic. MacMillan Tr. at 743:9-744:4.

64. Further, Dr. MacMillan admitted, the compounds he referred to as examples of "thiourea containing drugs" are either not di-substituted (unlike the Kirin Publication thiourea compounds), an insecticide (used to kill insects), or a compound that did not come to market. MacMillan Tr. at 745:10-746:13.

65. Thus, a POSA would have deprioritized the Kirin Publication compounds containing a thiourea functional group. Lepore Tr. at 437:12-20.

66. After deprioritizing the Kirin Publication thiourea compounds, a POSA would have evaluated the most potent non-thiourea compound: Example 269 (a malonamide compound). Lepore Tr. at 437:21-438:5. Dr. MacMillan agreed. MacMillan Tr. at 747:2-7.

67. A POSA would have recognized that Kirin Example 269 was potent (IC_{50} of 12.5 nM), did not raise thiourea toxicity concerns, and had the potential for irreversible inhibition because it contained a malonamide group. Lepore Tr. at 438:6-15; MacMillan Tr. at 747:5-10.

68. As Dr. MacMillan admitted, a POSA would have also noted that the molecular weight of Kirin Example 269 was well over the Lipinski limit. MacMillan Tr. at 753:25-754:5.

69. Kirin Example 269 did not fit well with the Lipinski Rule of 5, because of its molecular weight and because its Log *P* value was at the limit set by the Rule of 5. Lepore Tr. at 438:6-24. Therefore, a POSA would have continued to evaluate other potent compounds disclosed in the Kirin Publication to select as a lead compound. Lepore Tr. at 438:25-439:11.

70. A POSA would have evaluated the next potent non-thiourea compounds: two urea compounds and one malonamide compound (Kirin Example 5). Lepore Tr. at 438:25-439:11; DTX-6.20-50; DTX-6.387-89.

71. These three compounds all had comparable potency (IC_{50} of 15-20 nM), but the urea compounds did not present the same opportunity for irreversible inhibition. Lepore Tr. at 438:25-439:11. Therefore, a POSA would have next evaluated Kirin Example 5 as a potential lead compound. Lepore Tr. at 438:25-439:11.

72. A POSA would have recognized that Kirin Example 5 did not raise thiourea toxicity concerns, had the potential for irreversible inhibition because it contained a malonamide group,

was the second most potent malonamide compound (IC_{50}=18.9 nM), did not exceed any of the four criteria of the Rule of 5, and thus was predicted to have good oral bioavailability. Lepore Tr. at 439:12-25, 441:5-16.

73. As Dr. MacMillan admitted, Kirin Example 5 is one of the few compounds in the Kirin Publication with a molecular weight below the Lipinski cutoff. McMillan Tr. at 754:19-22.

74. Further, Dr. MacMillan agreed a POSA would have considered Kirin Example 5 to be a potent c-Met inhibitor. MacMillan Tr. at 741:1-11.

75. While Kirin Example 5 is not one of the "most preferred" compounds in the Kirin Publication, Dr. MacMillan agreed a POSA would not have been limited to the five "most preferred" compounds when selecting a lead. MacMillan Tr. at 749:7-13, 750:2-8.

76. When selecting a lead, a POSA would have prioritized Kirin Example 5, a "particularly preferred" compound, over the "most preferred" compounds, Kirin Examples 1, 2, 3, 11, and 268. Lepore Tr. at 440:1-17; DTX-6.50. This is because Kirin Examples 1, 2, and 268 are thiourea compounds that would have raised toxicity concerns. Lepore Tr. at 440:18-21. Kirin Examples 3, 11, and 268 were less potent than Kirin Example 5. Lepore Tr. 440:22-441:4; *see also* MacMillan Tr. at 757:22-24. And Kirin Example 11 was not fully compatible with the Rule of 5. Lepore Tr. at 440:22-441:4.

77. Thus, Kirin Example 5 was an obvious lead compound from among a small and finite number of potent compounds disclosed in the Kirin publication. Lepore Tr. at 441:5-16.

C. A POSA Would Have Been Motivated To Modify Kirin Example 5 And Prepare Cabozantinib With A Reasonable Expectation Of Obtaining A c-Met Inhibitor

78. A POSA would have been motivated to modify Kirin Example 5 because the data disclosed in Williams suggested that a malonamide containing compound (e.g., Kirin Example 5)

could potentially convert into a very small amount of an unstable form. Lepore Tr. at 441:25-442:15, DTX-23.2; *see also* Mann Tr. at 266:7-20; Bannen Tr. at 262:24-263:9.

79. Dr. MacMillan agreed with this potential stability issue and agreed that a POSA would have been motivated to make a more stable compound. MacMillan Tr. at 758:13-759:5.

80. To address this potential issue, a POSA would have been motivated to replace the two carbon-hydrogen bonds in the middle of the malonamide group. Lepore Tr. at 442:16-24.

81. When modifying Kirin Example 5, a POSA would have been guided by Lipinski's Rule of 5. Lepore Tr. at 442:25-443:7.

82. Thus, a POSA would have chosen a group that does not add hydrogen bond donors or hydrogen bond acceptors, and a small group that does not unduly increase the molecular weight of the compound. Lepore Tr. at 443:8-444:4. These considerations would have led a POSA to replace the two hydrogens with two carbons connected to each other with a bond, thus forming a geminal cyclopropyl group. *Id.*

83. Introducing the geminal cyclopropyl group would have addressed Kirin Example 5's potential instability issue. Lepore Tr. at 444:9-15; Bannen Tr. at 263:13-20.

84. Dr. MacMillan agreed that cyclopropyl was one of the groups a POSA could have added to Kirin Example 5. MacMillan Tr. at 762:12-18.

85. Thus, a POSA would have been motivated to incorporate a geminal cyclopropyl group into Kirin Example 5 "mainly as a blocking" group, to address the potential instability issue. Lepore Tr. at 449:4-9.

86. Further, a POSA would have recognized that introducing a geminal cyclopropyl group had the additional potential of creating an irreversible inhibitor, which would have further motivated a POSA to perform this modification. Lepore Tr. at 443:24-444:1, 444:5-8. First, the

prior art taught several advantages of irreversible inhibitors, such as reducing the amount and frequency of doses and reducing undesired side effect. Lepore Tr. at 444:16-445:3.

87. Further, Kelner taught MGI 114, a cyclopropyl containing compound, was in phase II clinical trial for treating solid tumors, and McMorris taught a mechanism by which such compounds irreversibly inhibited their biological targets. Lepore Tr. at 445:16-447:5, DTX-27.1 (Abstract, Figure 1), DTX-25.4 (Scheme 1). A POSA would have understood that a geminal cyclopropyl analog of Kirin Example 5 could similarly irreversibly inhibit c-Met, assuming c-Met had a properly located nucleophile ("molecular hook"). Lepore Tr. at 447:6-16, 461:3-6.

88. Thus, the "secondary benefit" of creating a potential irreversible inhibitor would have further motivated a POSA to incorporate a geminal cyclopropyl group into Kirin Example 5. Lepore Tr. at 449:9-12.

89. Table 2 of the Kirin Publication disclosed that compounds with geminal dimethyl substitutions on the malonamide group (e.g., Kirin Example 104) inhibited c-Met. Lepore Tr. at 448:2-20; DTX-6.387. It is undisputed that a geminal cyclopropyl is smaller than a geminal dimethyl group. Lepore Tr. at 448:12-13; MacMillan Tr. at 764:13-16. Thus, a POSA would have reasonably expected the geminal cyclopropyl analog of Kirin Example 5 (i.e., cabozantinib) would continue to inhibit c-Met. Lepore Tr. at 448:2-449:3, 449:12-16.

90. While Dr. MacMillan speculated that a geminal cyclopropyl substitution could reduce the potency of Example 5, MacMillan Tr. at 709:21-13, 709:23-711:4, he did not testify that a POSA would have expected this substitution to cause the molecule to stop inhibiting c-Met.

91. While a POSA could not have guaranteed the development of a successful cancer drug, as Dr. MacMillan admitted, this would not have stopped a POSA from selecting and testing

lead compounds, or from trying to develop a compound that would be successful. MacMillan Tr. at 728:3-20.

92. Thus, a POSA would have had a reasonable expectation of success in modifying Kirin Example 5 to arrive at cabozantinib, the compound claimed in the asserted claim 5 of the '473 patent. Lepore Tr. at 447:21-449:2.

D. There Are No Objective Indicia That Support Non-Obviousness

1. Cabozantinib has not satisfied a long-felt, unmet need

93. At trial, Exelixis did not clearly identify the long-felt unmet need that cabozantinib has allegedly met. At one point, Dr. George testified that cabozantinib has met a long-felt unmet need for improved therapy options over chemotherapy. George Tr. at 606:12-18. But he admitted that Cabometyx (which contains cabozantinib as the active ingredient) does not "fully fill [this] unmet need," and that it only "fills it in part." George Tr. at 606:19-24; *id.* at 588:12-14 (testifying that some patients cannot tolerate Cabometyx). Thus, cabozantinib has not met this need.

94. At another point, Dr. George testified that cabozantinib has met a long-felt unmet need for "new" or "more" options for treating RCC, HCC, and thyroid cancers. George Tr. at 572:24-573:21. It is, however, undisputed that there is still a need for new, additional, and improved treatment options for these cancers. George Tr. at 611:10-13, 612:15-17, 542:21-543:3, 543:9-16, 543:25-544:6; Mega Tr. at 795:10-19, 795:20-796:11, 797:16-23, 798:14-20. Thus, cabozantinib has not satisfied this need.

95. While cabozantinib provided another treatment option for some renal, hepatocellular, and thyroid cancers, it was neither the first, nor the only, TKI available to treat these conditions. For example, the TKI pazopanib was approved to treat RCC prior to the approval of Cabometyx in 2016, which was originally approved as a second-line treatment. George Tr. at 612:23-613:7; D.I. 275-1 (Uncontested Facts) at ¶¶ 53, 57. Axitinib and sorafenib, which are

TKIs, and everolimus were also all available as second-line RCC treatments before Cabometyx was approved as a second-line treatment for RCC in 2016. George Tr. 613:8-17.

96. When Cabometyx was approved as a second-line treatment for HCC, in 2019, (D.I. 275-1 at ¶ 59), sorafenib had already been approved as a second-line HCC treatment for HCC. George Tr. at 613:21-614:1. Regorafenib was also approved as a second-line HCC treatment prior to Cabometyx. George Tr. at 614:2-6.

97. Similarly, when Cabometyx received approval for the treatment of DTC in 2021, (D.I. 275-1 at ¶ 61) lenvatinib and sorafenib were already both approved to treat DTC. George Tr. 614:10-18.

98. And, vandetanib was already available to treat MTC, (*id.* at 614:24–615:5) when Cometriq was approved to treat it in 2012. D.I. 275-1 at ¶¶ 62, 65.

99. The fact that additional treatment options entered the market for treating RCC after cabozantinib further shows cabozantinib did not satisfy a long-felt un-met need. For example, nivolumab, the first immunotherapeutic agent, received FDA approval after cabozantinib. Mega Tr. at 788:15-24. The focus in the RCC treatment field then changed to combination therapies that combined immunotherapeutic agents or a TKI and an immunotherapeutic agent. Mega Tr. at 788:15-24. In general, the treatment options approved after cabozantinib in general show improved outcomes compared to cabozantinib. Mega Tr. at 788:25-789:3.

100. Thus, it is not surprising that cabozantinib is not the only available or "preferred" treatment option for treating RCC. For example, the November 2021 NCCN Guidelines for treating kidney cancers show other "preferred" options in addition to treatment regimens including cabozantinib in both the first line and the subsequent line categories for treating clear cell RCC. Mega Tr. at 791:19-792:7, 793:8-795:9; DTX-118.14. Dr. George agreed. George Tr. at 610:13-

611:5. Notably, the other "preferred" treatment options are supported by the same, or higher, levels of evidence and consensus compared to those containing cabozantinib. Mega Tr. at 793:8-22, 795:1-9.

101. The NCCN Guidelines' "preferred" treatment options for patients with non-clear RCC are sunitinib, cabozantinib, and clinical trials. Mega Tr. at 795:20-796:11; DTX-118.15. Dr. George agreed. George Tr. at 611:3-9. The inclusion of clinical trials as one of the "preferred" treatment options further supports there is still a need for safe and effective treatment for patients with non-clear RCC. Mega Tr. at 795:20-796:11; DTX-118.15.

102. Dr. George testified that around 13,000 patients died of RCC in 2021. George Tr. at 542:25-543:3. This further supports that there is still a need for new, additional, or improved treatment options for treating patients with RCC. Mega Tr. at 795:10-19, 807:6-11.

103. The September 2021 NCCN Guidelines for treating liver cancers show cabozantinib did not satisfy a need for treating HCC. First, cabozantinib is not listed as a first line "preferred" or "other recommended" treatment option for treating HCC. Mega Tr. at 796:19-797:7; DTX-124.24.

104. Further, cabozantinib is not the only subsequent line "preferred" treatment option for treating HCC supported by category 1 evidence in the NCCN Guidelines. Mega Tr. at 797:8-15, DTX-124.24. Dr. George agreed. George Tr. at 612:10-14.

105. Dr. George testified that around 30,000 patients died from HCC in 2021. George Tr. at 543:13-16. As Dr. Mega testified, these numbers, which are expected to rise, further show there is still a need for new, additional, or improved options for treating patients with HCC. Mega Tr. at 797:16-23.

106. Turning to the differentiated thyroid cancer, cabozantinib is not indicated as a first line therapy, and is not the only treatment option in the second line space. Mega Tr. at 797:24-798:13 (testifying about other therapies that are available (such as BRAF) for patients with certain mutations).

107. Dr. George testified that around 2,000 patients died from thyroid cancer in 2021. George Tr. at 544:4-6. As Dr. Mega testified, metastatic thyroid cancers, which can afflict younger people, remains incurable. Mega Tr. at 798:14-20. Thus, there is still a need for new, additional, or improved treatment options for treating patients with thyroid cancers. Mega Tr. at 798:14-20.

108. Thus, Exelixis has not shown cabozantinib satisfied any long-felt unmet need.

2. Exelixis has not shown failure of others

109. At trial, Exelixis attempted to present evidence that cabozantinib's approval as a subsequent line therapy shows failure of others. George Tr. at 577:19-25. Exelixis, however, failed to proffer evidence that could support nonobviousness of the asserted claim 5 of the '473 patent.

110. First, Dr. George admitted he has not identified any failed attempt to synthesize cabozantinib or a its salt, the recited elements in claim 5. George Tr. at 616:6-11.

111. Dr. George also admitted he did not know why compounds disclosed in the Kirin Publication did not advance to market. George Tr. at 615:24-616:5.

112. Further, others did not fail in developing safe and effective therapies for treating cancers cabozantinib is indicated for. To the contrary, sorafenib, vandetanib, sunitinib, pazopanib, regorafenib, and lenvatinib, were developed before cabozantinib, and received FDA approved before cabozantinib. Mega Tr. at 798:21-799:19, 787:25-788:6.

113. Dr. George agreed that sunitinib, pazopanib, sorafenib, and vandetanib were disclosed in the prior art and were FDA approved before cabozantinib. George Tr. at 607:4-12, 612:24-613:2, 613:5-8, 613:22-614:2, 614:25-615:6.

114. Cabozantinib's approval as subsequent line therapy for treating certain cancers does not show failure of others. Mega Tr. at 799:13-19. For example, there are several other subsequent line treatment options available and recommended by the NCCN Guidelines for treating RCC and HCC. Mega Tr. at 799:13-19; *see* above at ¶¶ 92-93.

115. Further, like other available treatments, resistance develops in most patients treated with cabozantinib, who would subsequently need other treatment options. Mega Tr. at 787:25-788:6, 808:1-17, 816:6-17.

3. Exelixis has not shown commercial success

116. At trial, Exelixis attempted to present evidence that Cabometyx (which contains cabozantinib as the active ingredient) is a commercial success. Tate Tr. at 631:13-17. For the reasons explained below, Exelixis failed to present evidence supporting this conclusion.

117. Mr. Tate, Exelixis's expert, admitted that evidence of commercial success is relevant to nonobviousness because the law presumes an idea would have been successfully brought out to market sooner in response to market forces had the idea been obvious to a POSA. Tate Tr. at 649:23-650:4.

118. Dr. McDuff testified that Mr. Tate's conclusion that Cabometyx is a commercial success was not supported by any analysis addressing the core question of whether others would have developed a product sooner in response to market forces. McDuff Tr. at 770:10-21.

119. Specifically, Mr. Tate's analysis (i) lacked "comparisons to other products," (ii) lacked "evaluation of commercialization costs to bring the product to market," and (iii) relied on "uninformative market shares." McDuff Tr. at 770:22-771:4, 771:8-772:12; DTX-231.3.

120. With respect to the first shortcoming, Dr. McDuff testified that "there's no basis of comparison to know whether these sales are high, low, or somewhere in between," McDuff Tr. at 772:13-25. Exelixis should have provided comparisons to "other pharmaceutical products, other

cancer products, other kidney cancer or liver cancer products, projections . . . any comparison at all." McDuff Tr. at 773:1-5. Instead, Mr. Tate admitted that he did not compare profits or revenue of Cabometyx to the profits or revenue of any other product in the market. Tate Tr. at 644:20-23, 650:5-20.

121. Regarding the second shortcoming, Mr. Tate did not properly evaluate commercialization costs. As Dr. McDuff testified, Mr. Tate did not conduct any "analysis at all of the costs that were incurred between 2003 and 2016." McDuff Tr. at 774:22-775:4.

122. Mr. Tate's analysis beginning at the time of launch (2016) applied the "wrong perspective," because it fails to address whether others would have sought to develop this product before September 2003. McDuff Tr. at 775:5-21.

123. As Dr. McDuff testified, it is common to evaluate commercialization costs in the pharmaceutical industry both by businesses and in the academic publication. McDuff Tr. at 774:4-9. This is supported by the DiMasi and Grabowski textbook which shows a typical life cycle of a drug product includes an investment phase (shown on the left side of Figure 2.11), and the profits and sales that are earned after a product is launched (shown on the right side of Figure 2.11). DTX-200.21; McDuff Tr. at 774:10-23.

124. Mr. Tate admitted that he did not take into account the research and development cost when analyzing the profitability of Cabometyx, Tate Tr. at 650:5-10, despite the fact that the research and development OPEX has increased every year since Cabometyx was first launched, Tate Tr. at 653:20-654:2, and that research and development cost was the largest cost associated with Cometriq and Cabometyx as February 2022. Tate Tr. at 649:19-22.

125. Regarding the third shortcoming, Dr. McDuff testified that Mr. Tate's analysis "provides no guidance" on whether Cabometyx's market share is high or low, and whether the product is a commercial success. McDuff Tr. at 778:15-779:6.

126. For example, Mr. Tate referred to PTX-363. Tate Tr. at 633:6-634:19. But, as Dr. McDuff testified, Mr. Tate's testimony regarding PTX-363 did not show that Cabometyx has a market share of 38% in the RCC market because "[t]here are many more products that are used to treat RCC in addition to these four that are more than a dozen, in Mr. Tate's report," and because the data on prescriptions is broken down by product, not indication. McDuff Tr. at 776:11-777:3.

127. Instead, PTX-822.3 showed the total RCC market and that Cabometyx's market share is "declining over time, and as of the last quarter on the chart, it's around 11 percent." McDuff Tr. at 777:8-778:6.

128. Similarly, PTX-822.5 showed the first-line treatment for the RCC market and that Cabometyx's market share "is declining. And it declines to about 5 percent as of the latest quarter with data." McDuff Tr. at 778:7-12.

129. Dr. McDuff testified that Cabometyx does not have 100 percent market share for treating differentiated thyroid cancer, but it is the only product with "the exact . . . indication as Cabometyx." McDuff Tr. at 778:15-24.

130. Dr. McDuff also testified that Mr. Tate's testimony that PTX-364 shows 34,000 patients have been treated with Cabometyx is "not a helpful number for knowing whether others would have developed this product sooner" because it lacks context. McDuff Tr. at 779:11-24.

131. In sum, Dr. McDuff testified that Mr. Tate's analysis does not answer the question of whether others would have developed the product at issue sooner had it been obvious because

Mr. Tate's analysis of sales, return on investment, and market shares are "very limited." McDuff Tr. at 779:25-780:16.

4. Exelixis has not shown cabozantinib's inhibition profile would have been unexpected

132. At trial, Exelixis attempted to present evidence that cabozantinib's inhibition profile would have been unexpected. George Tr. at 579:8-13, 615:14-16.

133. Dr. George, however, admitted that he has not compared cabozantinib's inhibition profile to the inhibition profile of Kirin Example 5, or any other compounds disclosed in the Kirin Publication. George Tr. at 615:17-23.

134. Further, Exelixis's experts admitted that a compound's ability to inhibit multiple tyrosine kinases is an inherent property of the compound, McMillan Tr. at 731:21-732:3, which is a property a POSA would have been able to test before September 2003. George Tr. at 593:5-16.

135. Thus, Exelixis has not shown that cabozantinib's inhibition profile would have been unexpected in view of the prior art. Lepore Tr. at 451:10-23.

5. Simultaneous invention supports obviousness

136. Dr. Lepore testified that the prior (near simultaneous) and independent invention of compounds in the Kirin Publication that are similar to cabozantinib (e.g., Kirin Example 5) is objective evidence of obviousness. Lepore Tr. at 451:24-452:10.

137. Exelixis did not offer any evidence on this issue.

HEYMAN ENERIO
GATTUSO & HIRZEL LLP

/s/ Dominick T. Gattuso
Dominick T. Gattuso (#3630)
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorney for MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.

OF COUNSEL:

George C. Lombardi
Bryce A. Cooper
Kurt A. Mathas
Jason Z. Pesick
Kevin J. Boyle
WINSTON & STRAWN LLP
35 W. Wacker Drive,
Chicago, Illinois 60601-9703
(312) 558-5600

Noorossadat Torabi
WINSTON & STRAWN LLP
101 California Street
35th Floor
San Francisco, CA 94111-5840
(415) -591-1000

Dated: June 21, 2022